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Search History

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L11	L6 and (paraffin)	29	L11
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L4	calcium adj5 (vitamin adj1 d)	653	L4
L3	calcium adj10 (vitamin adj1 d)	823	L3
L2	calcium same (vitamin adj1 d) same peg	2	L2
L1	calcium same (vitamin adj1 d)	2325	L1

END OF SEARCH HISTORY

L8: Entry 27 of 60 File: USPT Jun 27, 2000

DOCUMENT-IDENTIFIER: US 6080431 A
TITLE: Combined calcium and vitamin supplements for bone growth

Abstract Text (1):
Nutritional mineral supplements comprising calcium citrate malate and vitamin D are disclosed. Estrogen can also be used with these supplements. These supplements, which provide at least 25% RDA of calcium and vitamin D are used in addition to the normal diet. These supplements are useful for increasing bone growth and for treating age-related bone loss in humans and animals.

Brief Summary Text (2):
The present invention relates to nutritional and therapeutic improvements in calcium supplements containing vitamin D. These supplements are useful for increasing bone growth and treating age-related bone loss. They can be used in conjunction with foods and beverages or taken as an oral solid or liquid supplement. The invention also relates to a method of building bone or treating bone loss in osteoporotic patients, post-menopausal women and/or elderly men.

Brief Summary Text (4):
Vitamin and mineral supplements for human and veterinary use are commonplace. Some diets, heavy physical exercise and disease conditions may require the intake of considerable quantities of minerals and vitamins apart from those generally obtained through what otherwise would be considered a normal diet. Calcium and vitamin supplementation is important primarily for those who have inadequate diets, including growing children. Older adults have an additional need for calcium to help prevent the bone loss which occurs as a normal consequence of the aging process. In particular, postmenopausal women need additional calcium due to hormonal changes which can accelerate the bone loss rate leading to a further diminishment in bone mass.

Brief Summary Text (5):
There are well-recognized problems associated with adding both calcium and vitamin D to foods and beverages. Some of these are taste; calcium tends to be chalky in flavor. In addition, the solubility of many calcium sources prevents them from being added to many beverages. Interactions of calcium with the food or beverage affect the stability and/or the bioavailabilty of the product. This invention provides a means for making such product.

Brief Summary Text (6):
This invention also relates to methods of building bone in humans and other animals, i.e., for the treatment of age-related bone loss and related disorders. In particular, this invention relates to such methods of treatment by administration of calcium, citrate and malate ions and vitamin D.

Brief Summary Text (7):
Calcium is the fifth most abundant element in the human body. It plays an important role in many physiological processes, including nerve and muscle functions. Not surprisingly, nutritional and metabolic deficiencies of calcium can have broad-ranging adverse effects. Since about 98% to 99% of the body's calcium is found in bone tissues, many of these adverse effects are manifested through deficiencies in

the structure, function and integrity of the skeletal system.

Brief Summary Text (8):
The most common metabolic bone disorder is osteoporosis. Osteoporosis can be generally defined as the reduction in the quantity of bone, either from the reduction in bone formation or the acceleration of bone resorption, in either event the result is a decrease in the amount of skeletal tissue and resultant bone fractures. In general, there are two types of osteoporosis: primary and secondary. "Secondary osteoporosis" is the result of an identifiable disease process or agent. However, approximately 90% of all osteoporosis cases are idiopathic "primary osteoporosis". Such primary osteoporosis includes postmenopausal osteoporosis, age-associated osteoporosis (affecting a majority of individuals over the age of 70 to 80), and idiopathic osteoporosis affecting middle-aged and younger men and women.

Brief Summary Text (9):
For some osteoporotic individuals the loss of bone tissue is sufficiently great so as to cause mechanical failure of the bone structure. Bone fractures often occur, for example, in the wrist, hip and spine of women suffering from postmenopausal osteoporosis. Kyphosis (abnormally increased curvature of the thoracic spine) may also result.

Brief Summary Text (10):
The mechanism of bone loss in osteoporotics is believed to involve an imbalance in the process of "bone remodeling". Bone remodeling occurs throughout life, renewing the skeleton and maintaining the strength of bone. Two reactions are involved, bone loss or resorption and bone growth or accretion. This remodeling occurs in a series of discrete pockets of activity in the bone. These pockets are lined with two different cell types called "osteoclasts" and "osteoblasts". Osteoclasts (bone dissolving or resorbing cells) are responsible for the resorption of a portion of bone within the bone matrix, during the resorption process. After resorption, the osteoclasts are followed by the appearance of osteoblasts (bone forming cells), which then refill the resorbed portion with new bone.

Brief Summary Text (11):
In young healthy adults, the rate at which the osteoclasts and osteoblasts are formed maintains a balance of bone resorption and bone formation. However, as a normal consequence of aging an imbalance in this remodeling process develops, resulting in loss of bone at a rate faster than the accretion of bone. As imbalance continues over time the reduction in bone mass and thus bone strength leads to fractures.

Brief Summary Text (18):
U.S. Pat. No. 3,992,555 issued to Kovacs (assigned Vitamins, Inc., 1976) describes food supplements prepared by mixing assimilable iron compounds, vitamins and minerals with a heated edible fat carrier. Calcium and vitamin D are among the minerals in the supplement.

Brief Summary Text (24):
Milk contains solubilized calcium and is often fortified with vitamin D. Milk's calcium is about 50% calcium citrate and 50% calcium phosphoprotein complexes.

Brief Summary Text (25):
The utility of these known supplements varies. Unlike agents (such as estrogen) which affect the metabolism of bone, calcium nutritional supplements have been thought to merely provide a source for calcium (which may or may not be properly absorbed and metabolized). See, for example, B. Riis et al., "Does Calcium Supplementation Prevent Postmenopausal Bone Loss?," New England J. of Medicine, 316, 173-177 (1987); L. Nilas et al., "Calcium Supplementation and Postmenopausal Bone Loss," British Medical Journal, 289, 1103-1106 (1984); and H. Spencer et al., "NIH Concensus Conference: Osteoporosis," Journal of Nutrition, 116, 316-319

(1986).

Brief Summary Text (26):
It has now been discovered, however, that the administration of mixtures of certain calcium salts, i.e. calcium citrate and malate, and vitamin D are effective for delaying age-related loss of bone. In particular, as compared to nutritional regimens known in the art, these methods afford greater efficacy in the treatment of age-related bone loss and related disorders.

Brief Summary Text (27):
It would be desirable, therefore, to have mixed calcium and vitamin D therapies which are compatible and nutritionally available. It would also be quite useful to have such supplements which could be added to food and beverage compositions without undesirably affecting organoleptic or aesthetic properties.

Brief Summary Text (28):
It is an object of the present invention to provide calcium mineral supplements which, when combined with vitamin D, provide bone growth and can be used to treat age-related bone loss or to correct the imbalance that occurs between bone formation and bone resorption.

Brief Summary Text (29):
It is a further object of this invention to provide foodstuffs, beverages and beverage concentrates which are supplemented with calcium and vitamin D therapies.

Brief Summary Text (32):
The supplements employ specific calcium salts of mixtures of citric and malic acids combined with vitamin D. Estrogen can be used in conjunction with any of these therapies. These supplements can be added to foods and beverages.

Brief Summary Text (33):
The present invention provides methods for building bone in a human or other animal subject, comprising administering to said subject a safe and effective amount of vitamin D and calcium citrate malate. The calcium citrate malate comprises a complex or a mixture of calcium salts having a ratio of moles of calcium to moles of citrate to moles malate of from about 2:1:1 to about 8:2:1. The combination is preferably administered in foods/beverage application or in a solid dosage form, i.e. a tablet.

Detailed Description Text (2):
The present invention relates to stable calcium and vitamin D supplements and supplemented foods and beverages including dry beverage mixes and to a method of building bone.

Detailed Description Text (3):
As used herein, the term "comprising" means various components can be conjointly employed in the calcium and vitamin D supplements, foods and beverages of the present invention. Accordingly, the terms "consisting essentially of" and "consisting of" are embodied in the term comprising.

Detailed Description Text (4):
By "nutritional" or "nutritionally-supplemental amount" herein is meant that the mineral and vitamin sources used in the practice of this invention provide a nourishing amount of vitamin D and calcium. This is supplemental or in addition to the amount found in the average diet. This supplemental amount will comprise at least 25% of the Recommended Dietary Allowance (RDA) of the daily intake of calcium and vitamin D. Preferably, at least 50% of the Recommended Dietary Allowance (RDA) will be provided. The RDA for vitamin and minerals is as defined in The United States of America (see Recommended Daily Dietary Allowance-Food and Nutrition Board, National Academy of Sciences-National Research Council).

Detailed Description Text (12):
Estrogen therapy can be used along with any of these regimens. The method herein also comprises coadministering from about 0.3 mg to about 6 mg of estrogen along with the calcium and vitamin D, and/or calcium and vitamin D along with calcitonin or etidronate (or diphosphonates). Preferably from 0.625 mg to about 1.25 mg of estrogen is taken daily. Any viable estrogen hormone replacement can be used.

Detailed Description Text (16):
It is essential to this supplementation that the calcium salts be soluble. This solubilization aids in making the calcium more readily bioavailable. It is equally important that both the calcium and vitamin D be bioavailable. To add this the ingredients should be solubilized and absorbed by the stomach and or intestine. Any excipients used should disintegrate easily so that the calcium and vitamin D are released. The choice of calcium salts and vitamin D depends upon the interaction of the salts in acid (stomach pH) solutions or basic (intestinal pH) solutions.

Detailed Description Text (33):
The calcium, citric and malic acids can be added with the vitamin D to a 100% fruit juice or a diluted fruit juice. The sugars present in the juice are useful sweeteners, and the juice can be the flavor component. Such beverages can contain from 5% to 100% juice. Preferably dilute juice beverages will have from 10% to 40% juice. Preferred juices for 100% juice products or diluted products are orange, cranberry, apple, pear, grape, raspberry, lemon, grapefruit, pineapple, banana, blackberry, blueberry and passion fruit juices and mixtures thereof.

Detailed Description Text (51):
When making a dry beverage, it is preferred to mix a powdered calcium citrate malate powder with the sugar or artificial sweeteners, vitamin D and flavors. Colors and colored coated sugars can be added. Dry chocolate milk beverages are preferred dry beverage mixes. These can be diluted either with water or milk. Milk provides additional vitamin D and calcium citrate. A typical formula for chocolate mixes is:

Detailed Description Text (55):
d) from about 0.6% to about 0.15% calcium citrate malate and from about 0.60 to about 30 micrograms vitamin D.

Detailed Description Text (57):
Solid forms include tablets, capsules, granules and bulk powders. Tablets may contain suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid oral dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, and coloring and flavoring agents. A preferred liquid dosage form contains calcium citrate malate and vitamin D in a juice-containing beverage or other beverage.

Detailed Description Text (58):
The calcium citrate malate and vitamin D therapy can be coadministered in one tablet, liquid, food or beverage or they can be administered separately. A tablet or capsule containing the vitamin D and a second tablet with the calcium citrate malate are easy to formulate and to swallow. Vitamin D could also be coadministered with a calcium citrate malate containing beverage.

Detailed Description Text (60):
Method of Building Bone

Detailed Description Text (61):
Various oral dosage forms of calcium citrate malate and vitamin D may be used in the present invention. Such dosage forms comprise a safe and effective amount of calcium citrate malate, vitamin D and a pharmaceutically acceptable carrier. Preferably the pharmaceutically acceptable carrier is present at a level of from about 0.1% to about 99%, preferably from about 0.1% to about 75%, by weight of the composition. Unit dosage forms (i.e., dosage forms containing an amount of calcium citrate malate suitable for administration in one single dose, according to sound medical practice) preferably contain from about 100 mg to about 1000 mg, preferably from about 100 mg to about 500 mg, more preferably from about 200 mg to about 300 mg of calcium (on an elemental basis).

Detailed Description Text (64):
Specifically, the present invention provides a method for building bone in a human or other animal subject, comprising administering to said subject a safe and effective amount of calcium citrate malate and vitamin D for a period of time sufficient to achieve an increase in the net skeletal mass of said subject. As used herein, "building bone" refers to a decrease in the net skeletal loss of bone of the subject treated and therefore a net skeletal increase in mass. The slowing of the rate of bone loss and the increase in growth rate occur simultaneously so the net bone density may stay the same. The increase in mass may be at any skeletal site, including spine, hip, long bones of arms or legs or in the skeleton as whole. Preferably, the net skeletal mass is increased by at least about 0.1%, more preferably at least about 1%.

Detailed Description Text (65):
The loss of bone is cumulative over a long period of time. Typically, lifetime loss in bone mass is about 35% in males and 50% in females. Thus, even though a net skeletal increase of as little as 0.5% in one year is not particularly critical, over 10 years this results in 5% more bone mass than would be present if bone loss continued at its usual rate.

Detailed Description Text (66):
"Administering" refers to any method which, in sound medical practice, delivers the vitamin D and calcium citrate malate used in this invention to the subject to be treated in such a manner so as to be effective in the building of bone.

Detailed Description Text (67):
The specific period of time sufficient to achieve an increase in the net skeletal mass of the subject may depend on a variety of factors. Such factors include, for example, the specific mineral formulation employed, the amount of minerals administered, the age and sex of the subject, the specific disorder to be treated, concomitant therapies employed (if any), the general physical health of the subject (including the presence of other disorders), the extent of bone loss in the individual, and the nutritional habits of the individual. Although the administration of even small quantities of calcium citrate malate and vitamin D may build bone, the net increase in bone mass may not be detectable for short periods of administration.

Detailed Description Text (68):
For the treatment of age-related bone loss, the calcium citrate malate and vitamin D are administered for at least about six months, preferably for at least about twelve months. Of course, such administration may be continued indefinitely, according to sound medical practice.

Detailed Description Text (69):
The methods of this invention may be employed in the treatment of any of a variety of disorders in which the building of bone is desired. Thus, preferably, the human or other animal "subject" of the methods of this invention is in need of a method for building bone, i.e., the subject has a disorder for which building of bone or

decrease in rate of bone resorption would be advantageous according to sound medical practice. Such disorders include, for example, bone fractures, reduced mass and disorders typified by bone loss, such as age-related bone loss and osteoporosis (both primary and secondary forms).

Detailed Description Text (70):
A preferred method of this invention is for the treatment of age-related bone loss.

Detailed Description Text (71):
In addition to estrogen therapy, other therapies can be used along with the calcium and vitamin D supplements of this invention. Preferred therapies include the administration of calcitonin or etidronate or other diphosphonates and aminodiphosphonates to the human subject.

Detailed Description Text (78):
The tablet formulation is made by thoroughly admixing the powders, and tabletting using a standard tablet press, to form tablets weighing approximately 1104 milligrams. The tablets are then coated, using a pan coater. The coating solution contains approximately 11% hydroxypropylmethyl cellulose, approximately 2% polyethylene glycol, approximately 3.5% colorant, and the balance of water.

Detailed Description Text (80):
At the beginning of the study and after one year the bone density of the spine and overall body bone density are measured by dual x-ray absorptiometry.

Detailed Description Text (81):
The change in the bone density of the spine is statistically significant and shows a net increase in bone density. The whole body bone density is not significantly different. While this means there was no gain in the whole body bone density, it also means that the women did not lose bone density over the year which is expected in normal post-menopausal women not taking calcium supplements. The CCM/placebo patients also did not lose bone in the spine or whole body, but they did not gain bone as did those taking vitamin D.

Detailed Description Paragraph Table (2):

	Percent Change in Bone Density After 1 Year	
	Spine	Whole Body
CCM + Placebo	0.15 .+-. 0.25	-0.08 .+-. 0.11
CCM + Vitamin D	0.85 .+-. 0.23	0.03 .+-. 0.12

Other Reference Publication (3):
Dawson--Hughes et al, A Controlled Trial of the Effect of Calcium Supplementation on Bone Density in Postmenopausal Women., New England Journal of Medicine, vol. 323 (13) pp. 878-883 (1990).

Other Reference Publication (10):
Riis et al., "Does calcium supplementation prevent postmenopausal bone loss?", New England Journal of Medicine, 316, pp. 173-177 (1987).

Other Reference Publication (11):
L. Nilas et al., "Calcium Supplementation and Postmenopausal bone loss", British Medical Journal, 289, pp. 1103-1106 (1984).

Other Reference Publication (17):
Dawson-Hughes, Dr. B., Effect of vitamin D Supplementation on wintertime and overall bone loss in healthy postmenopausal women, Annuals of Internal Medicine, vol. 115, pp. 505-512, 1991.

Other Reference Publication (25):

Kopitzki et al., Dietary Calcium and bone structure, Ernahrungs-Umschau, vol. 38, No. 5, 1991, pp. 186-191 (with English translation).

CLAIMS:

1. A method for building of bone in a human subject suffering from age-related bone loss comprising administering to said subject synergistic effective amounts of a mineral supplement comprising calcium citrate malate (CCM) and vitamin D.sub.3 for a sufficient period of time to increase the net skeletal mass of said subject by at least about 0.1%, wherein said calcium citrate malate is administered at a level from about 175 milligrams to about 2000 milligrams (on an elemental calcium basis) and wherein vitamin D.sub.3 is administered at a level of from 0.60 to 30 micrograms per day.

2. A method for building bone according to claim 1 wherein said calcium citrate malate is administered at a level of from about 250 to 1500 milligrams (on an elemental calcium basis), and wherein said vitamin D.sub.3 is administered at a level of from 2.5 to 25 micrograms per day.

3. A method for building of bone according to claim 2, wherein said period of time is at least about six months.

4. A method for building of bone according to claim 3, wherein said calcium citrate malate has a molar ratio of from about 2:1:1 to about 8:2:1.

5. A method for building of bone according to claim 1, wherein said mineral supplement is in a solid dosage form.

6. A method for building of bone according to claim 1, wherein said mineral supplement is in a liquid dosage form.

7. A method for building of bone according to claim 1, wherein said mineral supplement is administered as a beverage.

9. A method for the building of bone according to claim 1, wherein said period of time is sufficient to increase the net skeletal mass of said subject by at least about 0.5%.

13. A method of reducing fracture risk according to claim 1, in a human subject suffering from age-related bone loss comprising administering to said subject synergistic effective amounts of a supplement comprising calcium citrate malate and vitamin D.sub.3 for a sufficient period of time to increase the net skeletal mass of said subject by at least about 0.1%.

16. A mineral supplement for building bones comprising synergistic effective amounts of:

a) from 100 to 1000 mg of calcium (on an elemental basis) in the form of carboxylate selected from the group consisting of citrate, malate, lactate and mixtures thereof; and

b) from 0.60 to 25 micrograms of vitamin D.sub.3.

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L8: Entry 35 of 60 File: USPT Aug 31, 1999

US-PAT-NO: 5945412
DOCUMENT-IDENTIFIER: US 5945412 A

TITLE: Methods and compositions for preventing and treating bone loss

DATE-ISSUED: August 31, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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Kaufman; Keith D.	Westfield	NJ		
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NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Merck & Co., Inc.	Rahway	NJ			02

APPL-NO: 08/ 984425 [PALM]
DATE FILED: December 3, 1997

PARENT-CASE:
CROSS-REFERENCE TO RELATED APPLICATIONS The present application claims priority to U.S. Provisional Patent Application Ser. No. 60/032,634, filed Dec. 9, 1996, now abandoned.

INT-CL: [06] A61 K 31/58, A61 K 31/56, A61 K 31/44

US-CL-ISSUED: 514/176; 514/171, 514/284
US-CL-CURRENT: 514/176; 514/171, 514/284

FIELD-OF-SEARCH: 514/167, 514/176, 514/298, 514/324, 514/284, 514/171

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected Search ALL Clear

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	5512555	April 1996	Waldstreicher	514/168
☐	5543417	August 1996	Waldstreicher	514/284
☐	5550134	August 1996	Audia et al.	514/284
☐	5670514	September 1997	Audia et al.	514/298

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
WO 95/11254	April 1995	WO	

OTHER PUBLICATIONS

Durette et al., Database Caplus on STN, 1995.
Durette et al., Database Caplus on STN, 1993.
Rosen et al., Endocrinology 136 (1995), pp. 1381-1387, "Bone density is normal in male rats treated with finasteride."
Tollin et al., J. Clin. Endoc. Metab. 81 (1996), pp. 1031-1034, "Finasteride therapy does not alter bone turnover in men with benign prostatic hyperplasia. . . ".
Matzkin et al., Clin. Endocrinol. 37 (1992), pp. 432-436, "Prolonged treatment with finasteride (a 5alpha-reductase inhibitor) does not affect bone density and metabolism."

ART-UNIT: 164

PRIMARY-EXAMINER: Criares; Theodore J.

ATTY-AGENT-FIRM: Fitch; Catherine D. Winokur; Melvin

ABSTRACT:

The present invention provides for a method of inhibiting bone loss in a subject in need of such treatment comprising administration to the subject of a therapeutically effective amount of a compound of structural formula I: ##STR1## The present invention further provides for a method for treating and preventing osteoporosis and osteopenia and other diseases where inhibiting bone loss may be beneficial, including: Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, comprising administration of therapeutically effective amount of a compound of structural formula I to the subject.

Further, the present invention provides for compositions useful in the methods of the present invention, as well as a method of manufacture of a medicament useful for inhibiting bone loss and treating or preventing osteoporosis and osteopenia.

29 Claims, 0 Drawing figures

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L8: Entry 41 of 60 File: USPT Sep 8, 1998

DOCUMENT-IDENTIFIER: US 5804590 A
TITLE: Treatment and prophylaxis of osteoporosis

Brief Summary Text (6):
a decrease in renal calcium reabsorption due to a disorder in the vitamin D metabolism;

Brief Summary Text (8):
a decrease in bone metabolism due to chronically decreased magnesium and due to dysfunction of the parathyroid hormone;

Brief Summary Text (9):
a decrease in bone formation, or deficiency of insulin action.

Brief Summary Text (11):
Many thiazolidine derivatives are known for the treatment and prophylaxis of diabetes. Examples of such compounds are disclosed in EP 678 511, EP 676 398, EP 590 793, EP 543 662, EP 549 366, EP 549 365, EP 708 098 and U.S. Pat. No. 4,687,777. Of these, the compounds structurally closest to the compounds of the present invention are believed to be those disclosed in EP 676 398. Several of the prior art documents suggest that the compounds disclosed therein can be used for the treatment and/or prophylaxis of osteoporosis as well as of diabetes. However, a recent report [J. Bone & Mineral Research, 10(1), S361 (1995), Abstract of a paper entitled "Effects of thiazolidinediones on bone turnover in the rat" by C. Jennermann et al.] has suggested that, far from assisting in the treatment and/or prophylaxis of osteoporosis, these thiazolidine derivatives, particularly pioglitazone, one of the leading candidates for commercialisation, actually lead to bone loss, as assessed by a decrease in bone mineral density ("BMD"), thus increasing osteoporosis.

Brief Summary Text (12):
We have now found that these prior art compounds are capable of treating both osteoporosis and diabetes, although not simultaneously, since the anti-diabetic and anti-osteoporosis effects are exhibited at different dosages. Specifically, the dosages of the prior art compounds referred to above at which they are effective against osteoporosis are significantly lower than those required for the treatment of diabetes. Indeed, at the doses at which these prior art compounds are effective against diabetes, they cause a reduction in bone mineral density. At the doses at which they are effective against osteoporosis, they are ineffective, or only partially effective against diabetes. Since, as explained above, diabetes and osteoporosis are often seen simultaneously in the same patient, the physician would have the choice of either treating the diabetes and not treating osteoporosis with these drugs (and often running the risk of aggravating the osteoporosis) or treating the osteoporosis with these drugs, but in a dose not sufficient to treat the diabetes. Effectively, this means that patients with both osteoporosis and diabetes cannot be treated for either disorder with these drugs.

Brief Summary Text (103):
The compounds of the present invention may be administered alone or in admixture with any known additives commonly used in the field of drug preparation such as

vehicles, binders, disintegrators, lubricants, solubilizers, corrigents and coating agents. Such preparations may be obtained by known means.

Brief Summary Text (104):
When tablets are to be prepared, carriers which are widely known in this field can be employed, for example: vehicles such as lactose, sucrose, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose and silicic acid; binders such as water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatine solution, carboxymethyl cellulose, purified shellac, methyl cellulose, potassium phosphate and polyvinylpyrrolidone; disintegrators such as dry starch, sodium alginate, agar powder, laminaran powder, sodium bicarbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium laurylsulfate, stearic acid monoglyceride, starch and lactose; disintegration inhibitors such as sucrose, stearine, cacao oil and hydrogenated oil; absorption accelerators such as quaternary ammonium bases and sodium laurylsulfate; humectants such as glycerin and starch; adsorbers such as starch, lactose, kaolin, bentonite and colloidal silicic acid; and lubricants such as purified talc, a salt of stearic acid, powdery boric acid and polyethylene glycol. In addition, the tablets can be, if necessary, prepared as ordinary coated tablets such as sugar-coated tablets, gelatine-coated tablets, enteric coated tablets, film-coated tablets, or as double-layer tablets or multi-layer tablets.

Brief Summary Text (105):
When pills are to be prepared, carriers which are widely known in this field can be employed, for example: vehicles such as glucose, lactose, starch, cacao oil, hardened vegetable oil, kaolin and talc; binders such as gum arabic, tragacanth powder, gelatine and ethanol; and disintegrators such as laminaran agar.

Brief Summary Text (106):
When suppositories are to be prepared, carriers which are widely known in this field can be employed, for example: polyethylene glycol, cacao oil, a higher alcohol, a higher alcohol ester, gelatine and semi-synthetic glyceride.

Brief Summary Text (111):
Osteoporosis may be assessed by a measurement of bone mineral density. Bone mineral density can be measured according to the method reported, for example, in Radioisotope, 37, (9), 521-524 (1988) or in Rinsho-Hoshasen, 35, (1), 41-48 (1990).

Brief Summary Text (112):
Alternatively, bone mineral density can be measured using the simple photon absorption method [Science, 142, 230-236 (1963)] or the quantitative CT method [Invest. Radiol. 12, 541-551 (1977)].

Detailed Description Text (3):
Measurement of Bone Mineral Density

Detailed Description Text (8):
Compound No. 1, or 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl] thiazolidin- 2,4-dione, also known as "troglitazone", was administered to 6 week old ZDF rats, by mixing it into F2 powdery feed in an amount of 0.2% w/w for a period of 13 weeks. The mean dosage was 165 mg/kg/day. At this dose, diabetes is fully controlled. At 19 weeks of age, the rats were sacrificed by ether anesthesia followed by blood-letting from the abdominal aorta. The femoral bones were excised to measure their bone mineral density. For the measurement by X ray, Bone Mineral Density Measuring Apparatus (DCS-600R, Aloka, Japan) was employed.

Detailed Description Text (10):
As is clearly shown in Table 2, the thiazolidine derivatives of the present invention and pharmaceutically acceptable salts thereof showed an excellent

improvement on the bone mineral density.

Detailed Description Text (12):
Comparison of Effects of Troglitazone and Pioglitazone on Bone Mineral Density

Detailed Description Text (22):
Comparison of Effects of Troglitazone and Pioglitazone on Bone Density

Detailed Description Paragraph Table (1):
TABLE 2 _____ Bone mineral density (mg/cm.sup.2)
Number of rats in group BMD _____ Normal group 7 187.3 .+-. 2.3*** Control ZDF group 7 164.6 .+-. 3.9 Test ZDF group 7 172.8 .+-. 7.2* _____ 1) The values of the bone mineral density are given by the mean value .+- standard error. 2) * and *** indicate significant differences from the value of control ZDF rats at $p < 0.05$ and $p < 0.001$ respectively.

Detailed Description Paragraph Table (2):
TABLE 3 _____ Bone mineral density (mg/cm.sup.2)
Number of rats in group BMD _____ Normal group 6 187.4 .+-. 1.5 Control ZDF group 6 157.0 .+-. 2.2 Troglitazone ZDF group 6 169.4 .+-. 1.1*** Pioglitazone ZDF group 6 149.3 .+-. 1.8* _____ 1) The values of the bone mineral density are given by the mean value .+- standard error. 2) * and *** indicate significant differences from the value of control ZDF rats at $p < 0.05$ and $p < 0.001$ respectively.

Detailed Description Paragraph Table (3):
TABLE 4 _____ Bone mineral density (mg/cm.sup.2)
Number of rats in group BMD _____ Normal group 10 153.4 .+-. 0.9 Control ZDF group 5 149.8 .+-. 1.0 Low troglitazone ZDF 5 156.6 .+-. 1.5*** group High troglitazone ZDF 5 159.8 .+-. 1.2*** group Low pioglitazone ZDF 5 151.2 .+-. 0.9 group High pioglitazone ZDF 5 151.2 .+-. 0.7 group _____ 1) The values of the bone mineral density are given by the mean value .+- standard error. 2) *** indicates a significant difference from the value of control ZDF rats at $p < 0.001$.

Other Reference Publication (2):
C. Jennermann et al, "Effects of Thiazolidinediones on Bone Turnover in the Rat", Journal of Bone and Mineral Research, vol. 10, Supplement 1, Aug. 1995.

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L8: Entry 46 of 60 File: USPT Dec 2, 1997

DOCUMENT-IDENTIFIER: US 5693615 A
TITLE: Therapeutic compositions for osteoinduction

Abstract Text (1):
A method for generating new bone growth in a mammal comprising administrating to the mammal a safe and effective amount of a Vitamin D compound in combination with a safe and effective amount of osteoinductive extract or at least one BMP.

Brief Summary Text (2):
The present invention relates to the field of osteoinduction (bone growth). Specifically, the present invention relates to novel therapeutic formulations comprising the administration of bone morphogenetic proteins and a Vitamin D compound, resulting in synergistic bone growth.

Brief Summary Text (4):
In healthy individuals bone growth generally proceeds normally and fractures heal without the need for pharmacologic intervention. Nonetheless, in certain instances bones may be weakened or may fail to heal properly. For example, healing may proceed slowly in the elderly and in patients undergoing treatment with corticosteroids, such as transplant patients and those being treated for chronic lung disease. Another example is osteoporosis. Osteoporosis is an abnormal loss of bony tissue often occurring in post-menopausal woman and elderly men. The disorder increases the risks of small fractures occurring in the bones, particularly the spine. At present, osteoporosis is treated mainly by supplements of calcium, vitamin D, estrogen, or calcitonin, a hormone which controls the body's use of calcium. Unfortunately, these treatments are merely preventative against the further loss of bone. There is a need in the art for treatments that go beyond the prevention of bone loss and promote bone formation and/or reverse bone loss.

Brief Summary Text (5):
(1989) "Bone Morphogenic Proteins and Vitamin D", Nutrition Reviews, Vol. 47, pp. 364-366 concludes that Vitamin D in the diet prevents the loss of the osteoinductive activity of bone matrix.

Brief Summary Text (6):
Turner, R. T., J. Farley, J. J. Vandersteenhoven, S. Epstein, N. H. Bell, and D. J. Baylink, (1988) "Demonstration of Reduced Mitogenic and Osteoinductive Activities in Demineralized Allogeneic Bone Matrix from Vitamin D-deficient Rats", The Journal of Clinical Investigation, Inc., Vol. 82, pp. 212-217, discloses the implantation of demineralized bone matrix from Vitamin D-deficient rats into normal rats. The demineralized bone matrix from Vitamin D-deficient rats did not promote osteoinduction as effectively as demineralized bone matrix from normal rats.

Brief Summary Text (7):
Sampath, T. K., S. Weintraub, and A. H. Reddi, (1984) "Extra-cellular Matrix Proteins Involved in bone Induction are Vitamin D Dependent", Biochemical and Biophysical Research Communications, Vol. 124, pp. 829-835, discloses a study involving implantation of demineralized bone matrix from normal rats and demineralized bone matrix from rachitic rats wherein the rachitic bone matrix did not induce bone growth while the normal bone matrix did. The study concluded that

these results demonstrate that Vitamin D is necessary to produce bone inductive proteins in the bone matrix of a living rat.

Brief Summary Text (8):
U.S. Pat. No. 4,761,471, Urist, assigned to the Regents of the University of California, issued Aug. 2, 1988, discloses a bone morphogenetic protein composition comprising BMP factor and BMP associated protein having a molecular weight of 34,000 daltons. Use of such factors and compositions to induce bone formation in mammals is also disclosed.

Brief Summary Text (9):
U.S. Pat. No. 4,455,256, Urist, assigned to the Regents of the University of California, issued Jun. 19, 1984, discloses a bone morphogenetic protein having a molecular weight in the range of 1,000 to 100,000 daltons.

Brief Summary Text (10):
Various other bone morphogenetic proteins/factors, osteoinductive factors, osteogenic factors and other proteins/factors related to bone growth are disclosed in the following publications: U.S. Pat. No. 4,968,590, Kubersampath and Rueger, issued Nov. 6, 1990; U.S. Pat. No. 4,698,328, Neer, Potts and Slovik, issued Oct. 6, 1987; U.S. Pat. No. 4,877,864, Wang, Wozney and Rosen, issued Oct. 31, 1989; U.S. Pat. No. 4,861,757, Antoniades, Lynch and Williams, issued Aug. 29, 1989; U.S. Pat. No. 4,810,691, Seyedin, Thomas, Bentz, Ellingsworth and Armstrong, issued Mar. 7, 1989; U.S. Pat. No. 4,804,744, Sen, issued Feb. 14, 1989; U.S. Pat. No. 4,795,804, Urist, issued Jan. 3, 1989; U.S. Pat. No. 4,789,663, Wallace, Smestad, McPherson, Piez and Ross, issued Dec. 6, 1988; U.S. Pat. No. 4,789,732, Urist, issued Dec. 6, 1988; U.S. Pat. No. 4,774,322, Seyedin, Thomas, Bentz, Ellingsworth and Armstrong, issued Sep. 27, 1988; U.S. Pat. No. 4,698,328, Neer and Slovik, issued Oct. 6, 1987; U.S. Pat. No. 4,627,982, Seydin and Thomas, issued Dec. 9, 1986; U.S. Pat. No. 4,619,989, Urist, issued Oct. 28, 1986; U.S. Pat. No. 4,596,574, Urist, issued Jun. 24, 1986; U.S. Pat. No. 4,563,489, Urist, issued Jan. 7, 1986; U.S. Pat. No. 4,563,350, Nathan, Seyedin and Bentz, issued Jan. 7, 1986; U.S. Pat. No. 4,526,909, Urist, issued Jul. 2, 1985; U.S. Pat. No. 4,434,894, Seyedin and Thomas, issued Feb. 23, 1984; U.S. Pat. No. 4,294,753, Urist, issued Oct. 13, 1981; European Patent Application 349 048, Bab, Muhlrad, Gazit and Shteyer, published Jan. 3, 1990; European Patent Application 309 241, Chu, Nathan and Seyedin, published Mar. 29, 1989; European Patent Application 336 760, Bentz, Nathan, Rosen, Dasch and Seyedin, published Oct. 11, 1989; European Patent Application 145 155, Sen, published Jul. 10, 1985; World Patent Application 89/10934, Roos, Burns, Guy and McKnight, published Nov. 16, 1989; World Patent Applications 89/09787 and 89/09788, Oppermann, Kubersampath, Rueger and Ozkaynak, published Oct. 19, 1989; and World Patent Application 88/00205, Wang, Wozney and Rosen, published Jan. 14, 1988.

Brief Summary Text (12):
It is an object of the present invention to provide a method for generating new bone growth in a mammal.

Brief Summary Text (13):
It is a further object of the present invention to provide a pharmaceutical composition which can be used to generate new bone growth in a mammal.

Brief Summary Text (15):
The present invention relates to a method of generating new bone growth in mammals comprising administration to a mammal a combination of a safe and effective amount of a Vitamin D compound, and a safe and effective amount of one or more BMPs or osteoinductive extract comprising one or more BMPs.

Brief Summary Text (16):
The present invention further relates to a composition for generating new bone

growth in mammals comprising a safe and effective amount of a Vitamin D compound; a safe and effective amount of a BMP or osteoinductive extract comprising one or more BMPs; and a pharmaceutically-acceptable carrier.

Brief Summary Text (18):
The present invention comprises the administration to a mammal of a combination of a safe and effective amount of a Vitamin D compound and a safe and effective amount of one or more BMPs or an osteoinductive extract comprising one or more BMPs. It has been determined that treatment with a Vitamin D compound, BMP or osteoinductive extract alone increases bone growth. Surprisingly, it has been further determined that treatment with a Vitamin D compound in combination with osteoinductive extract or in combination with at least one BMP results in a level of new bone growth greater than that achieved through administration of the BMP, osteoinductive extract or Vitamin D compound alone. Subjects in need of such treatment suffer from a variety of ailments which may be treated via this procedure, including but not limited to, bone fractures (closed and open), non-union fractures, congenital defects, as an adjunct in plastic surgery, in treating oncological resections, all diseases classified as osteoporosis, rheumetoid arthritis, osteoarthritis, septic arthritis, rickets, organic incorporation of prosthetic joints and dental implants, periodontal disease and defects, as well as osteopenic and osteomalacic conditions and disease.

Brief Summary Text (20):
As used herein, "fracture reduction" means the restoration of a bone fracture by surgical or manipulative means to its normal anatomical relation.

Brief Summary Text (21):
As used herein, "BMP" means bone morphogenetic protein.

Brief Summary Text (24):
As used herein "regional treatment" includes treating bone fractures (closed and open), treating non-union fractures, treating congenital defects, as an adjunct treatment to plastic surgery, treating oncological resections, organic incorporation of prosthetic joints, organic incorporation of dental implants, and treatment of periodontal disease and defects.

Brief Summary Text (28):
As used herein, "mineralized tissue" means bone and teeth.

Brief Summary Text (35):
Bone Morphogenetic Proteins

Brief Summary Text (36):
In one embodiment of the present invention, a Vitamin D compound is administered in combination with one or more BMPs to generate new bone growth in a mammal. These BMPs are preferably selected from the group consisting of BMP-1, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 and BMP-7.

Brief Summary Text (50):
Another component of the invention is an osteoinductive extract. As used herein, "osteoinductive extract" means a chemical extract of bone, comprising one or more various bone morphogenetic proteins, including, but not limited to, BMP-1, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 and BMP-7, wherein each BMP has a molecular weight of from about 28,000 to about 40,000 daltons.

Brief Summary Text (53):
Snip the skin at the ankles of a 7-8 week old Long-Evans rat (Charles River laboratories, Wilmington, Mass.). Remove both tibiae and place in cold water. Rinse the bone with distilled water to remove non-osseous tissue (tissue other than bone). Allow the bone to air dry. Grind the bones by placing in an Osterizer (Oster

Commercial, Milwaukee, Wis.) blender with water and ice. With the blender set at "liquefy" speed, continue to add bone. Allow the blended material to settle for a few minutes. Decant the liquid layer. Place the solid layer on a stirring plate and add distilled water to wash. Continue washing until the distilled water washes clear. Once the distilled water is clear, add ice and stir. Add 1 ml of 1 mM of phenylmethylsulfonyl fluoride (PMSF). Wash for 1 hour adding ice frequently. Repeat with a second water wash. Place the sample in an ice water bath on a stirring plate. Defat with absolute ethanol, then defat twice with ethyl ether. Spread bone material onto glass petri dishes. Allow the bone chips to air dry overnight.

Brief Summary Text (54):
Weigh the bone chips following the overnight drying, Using a sieve (U.S.A. Standard Sieve Series, Newark Wire Cloth Co., Newark, N.J.; sieve #40 retains particles greater than 425 mm and sieve #170 retains particles greater than 90 mm), isolate the bone particles in the 90-425 um range. Grind any particles greater than 425 mm in a MicroMill (Scienceware Bel-Art Products, Pequannock, N.J.) for 1 minute adding dry ice to the bone particles to keep the material cold. Repeat the sieving and MicroMill grinding steps of the greater than 425 mm particles until the amount of total recovery is greater than 2/3 of the initial weight of the bone. Store the particles at 4.degree. C. until the next step. Weigh the particles isolated thus far. For each gram of particles, add 25 ml of 0.6N HCl. Stir vigorously at 4.degree. C. for 2 hours. After 2 hours, stop stirring and allow the particles to settle. Decant the HCl. Add fresh 0.6N HCl and stir again for 2 hours. Decant the HCl and add fresh 0.6N HCl a third time and stir for two hours. Decant the HCl and rinse with distilled water. Using litmus paper, check the pH of the water for the presence of HCl. Continue rinsing with distilled water until the pH is between about 5 and 5.5. Rinse the bone particles with ethanol three times. Swirl, allow to settle, and remove the supernatant. Rinse the bone particles with ethyl ether three times as above. Dry overnight in glass plates. The dried bone particles are referred to as "acid demineralized bone particles".

Brief Summary Text (55):
The acid demineralized bone particles are deproteinized as follows: Weigh the material following the overnight drying. For each gram of material, add a solution of 30 ml 4M guanidine-HCl, 10 mM Tris and 1.0 mM PMSF pH 6.4 to the bone material in a beaker. Extract for 16 hours at 4.degree. with vigorous stirring. Following the 16 hour extraction, cease stirring and allow the material to settle. Pour off the guanidine solution and save. Extract the material a second time for 6-7 hours using fresh guanidine-HCl solution. Following the extraction, pour off the solution and combine with the previously saved solution. The bone particles are now demineralized and deproteinized.

Brief Summary Text (58):
The pooled CM-Sepharose fractions are dialyzed three times for 24 hours each against 1% acetic acid. The dialysate is lyophilized to dryness and the protein pellet dissolved into 30 ml of 6M urea, 0.5M NaCl, 25 mM Na phosphate, pH 7.4. The sample is applied on a column of chelating Sepharose charged with zinc and equilibrated with the above buffer. The column is washed with the above buffer and then eluted with a gradient from 6M urea, 0.5M NaCl, 25 mM Na phosphate, pH 7.4 to 6M urea, 0.5M NaCl, 25 mM Na acetate, pH 4.6. Aliquots of each fraction are labeled with 125I and analyzed by SDS gel electrophoresis. Aliquots (100 ml) of each fraction are combined with 400 ml of elution buffer, dialyzed against 1% acetic acid and assayed for activity. Highly purified molecular weight range (M.sub.r) 25-40 kD peptides are assayed in the bone induction assay.

Brief Summary Text (64):
Some examples of substances which can serve as pharmaceutically-acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethylcellulose, ethylcellulose, cellulose acetate; powdered tragacanth;

malt; gelatin; talc; stearic acid; magnesium stearate; calcium sulfate; vegetable oils such a peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; sugar; alginic acid; pyrogen-free water; isotonic saline; phosphate buffer solutions; cocoa butter (suppository base); emulsifiers, such as the TWEENS.RTM.; as well as other non-toxic compatible substances used in pharmaceutical formulations. Wetting agents and lubricants such as sodium lauryl sulfate, as well as coloring agents, flavoring agents, excipients, tableting agents, stabilizers, antioxidants, and preservatives, can also be present. Other compatible pharmaceutical additives and actives (e.g., NSAI drugs; pain killers; muscle relaxants) may be included in the pharmaceutically-acceptable carrier for use in the compositions of the present invention. For example, art-known local anesthetics may be included in the pharmaceutically-acceptable carrier (e.g., benzyl alcohol; NOVOCAINE.RTM.; lidocaine).

Brief Summary Text (65):
Additional examples of carriers include collagen, demineralized bone particles, ceramic and metallic implant materials, collagen membrane and bone grafts (isogenic or allogenic).

Brief Summary Text (71):
Preferably, the vitamin D compound is administered via an oral dose form. Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules, bulk powders and microcapsules of the drug. These oral forms comprise a safe and effective amount, usually at least about 0.5%, and preferably from about 1% to about 10% of the compound of the present invention. Tablets can be compressed, enteric-coated, sugar-coated or filmcoated containing suitable binders, lubricants, surfactants, diluents, disintegrating agents, coloring agents, flavoring agents, preservatives, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous and nonaqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents, and flavoring agents. Preferred carriers for oral administration include gelatin and propylene glycol. Specific examples of pharmaceutically-acceptable carriers and excipients that may be used in formulating oral dosage forms containing compounds of the present invention are described in U.S. Pat. No. 3,903,297, Robert, issued Sep. 2, 1975, incorporated by reference herein. Techniques and compositions for making solid oral dosage forms are described in Marshall, "Solid Oral Dosage Forms," MODERN PHARMACEUTICS, Vol. 7, (Banker and Rhodes, editors), 359-427 (1979), incorporated herein by reference. Techniques and compositions for making tablets (compressed, formulas and molded), capsules (hard and soft gelatin) and pills are described in REMINGTON'S PHARMACEUTICAL SCIENCES (Arthur Osol, editor), 1553-1593 (1980), incorporated herein by reference.

Brief Summary Text (74):
Components of the topical-oral carrier are suitable for administration to the oral cavity of a human or lower animal and are compatible with one another and the other components, especially the Vitamin D compound and osteoinductive extract or BMP, used in an oral composition of the subject invention. Preferred topical-oral carriers thus provide the desired characteristics for toothpastes, tooth gels, tooth powders, mouthwashes, mouthsprays, prophylaxis pastes, dental treatment solutions, and the like. The topical-oral carriers of the subject invention comprise components typically used in such compositions which are well known to a skilled practitioner. Such components include, but are not limited to anticaries agents, antiplaque agents, anticalculus agents, dental abrasives, surfactants, flavoring agents, sweetening agents, binders, humectants, thickening agents, buffering agents, preservatives, coloring agents and pigments, ethanol, and water.

Brief Summary Text (80):

The active components of the present invention are also useful when injected. The dosage of the active components of the present invention which is both safe and effective to provide bone growth activity will vary with the particular condition being treated, the severity of the condition, the duration of treatment, the specific mixture of compounds employed and its usage concentration, and like factors within the specific knowledge and expertise of the attending physician and commensurate with a reasonable benefit/risk ratio associated with the use of any drug compound. In addition, lower dosages will be utilized when only local or minor bone growth is desired, whereas higher dosages will be utilized when general or major bone growth is desired.

Detailed Description Text (3):
An injectable composition comprising the osteoinductive extract and an oral composition comprising 1,25-dihydroxy Vitamin D.sub.3 for bone fracture repair is prepared by combining the following components utilizing conventional mixing techniques.

Detailed Description Text (6):
An injectable composition for bone fracture repair is prepared by combining the following components utilizing conventional mixing techniques.

Detailed Description Text (9):
A composition for inducing bone growth following reconstructive surgery is prepared by combining the following components utilizing conventional mixing techniques.

Detailed Description Text (10):
0.1 cc of the composition per cm.sup.2 of surface area of surgically reconstructed bone is deposited directly onto the bone surface.

Detailed Description Text (12):
A composition for accelerating the healing and providing a stronger bond between natural bone and an artificial prosthesis is prepared by combining the following components utilizing conventional mixing techniques.

Detailed Description Text (13):
0.1 cc of the composition per cm.sup.2 surface area of natural bone proximate to the prosthesis is deposited directly onto the natural bone.

Detailed Description Text (16):
After the patient is prepared using conventional periodontal surgical therapy 0.1 cc of the composition per exposed tooth is deposited into the surgery site. Soft tissue flaps are then sutured to close the surgical site. This treatment is useful for restoring alveolar and supporting bone in the periodontium lost by disease.

Detailed Description Text (21):
A composition for inducing bone growth of a non-union fracture is prepared by combining the following components utilizing conventional mixing techniques. As used herein, "non-union fracture" means a fracture that has failed to heal normally.

Detailed Description Text (22):
At the time of fracture reduction, a sufficient quantity of the above composition is deposited directly into the non-union site thereby filling in any bone deficit.

Detailed Description Paragraph Table (7):
Percent by Weight Component of Composition
BMPA 0.004 1,25-dihydroxy vitamin D.sub.3 0.010 Acid demineralized bone particles 90.000 NaCl 0.900 Sterile water for injection q.s. 100.000

Other Reference Publication (1):
"Bone Morphogenic Proteins and Vitamin D", Nutrition Reviews, vol. 47, pp. 364-366 (1989).

Other Reference Publication (3):
Sampath, T.K., S. Wientroub and A.H. Reddi, "Extracellular Matrix Proteins Involved in Bone Induction Are Vitamin D Dependent", Biochemical and Biophysical Communications, vol. 124, No. 3, pp. 829-835 (Nov. 1984).

Other Reference Publication (4):
Turner, R.T., J. Farley, J.J. Vandersteenhoven, S. Epstein, N.H. Bell and D.J. Baylink "Demonstration of Reduced Mitogenic and Osteoinductive Activities in Demineralized Allogeneic Bone Matrix from Vitamin D-deficient Rats", The Journal of Clinical Investigation, Inc., vol. 82, pp. 212-217 (Jul. 1988).

Other Reference Publication (5):
Underwood, J.L. and H.F. DeLuca, "Vitamin D is Not Directly Necessary for Bone Growth and Mineralization", American Journal of Physiology, vol. 246, pp. E493-E498 (1984).

Other Reference Publication (6):
Wang, E.A., V. Rosen, J.S. D'Alessandro, M. Bauduy, P. Cordes, T. Harada, D.I. Israel, R.M. Hewick, K.M. Kerns, P. LaPan, D.P. Luxenberg, D. McQuiid, I.K. Moutsatsos, J. Nove and J.M. Wozney, "Recombinant Human Bone Morphogenetic Protein Induces Bone Formation", Wang, Proc. Natl. Acad. Sci. USA, vol. 87, pp. 2220-2224 (Mar. 1990).

Other Reference Publication (7):
Weintroub, S. and A.H. Reddi, "Vitamin D Metabolites and Endochondral Bone Development", Int. Congr. Ser.-Excerpta Med., vol. 589, pp. 211-217 (1991).

Other Reference Publication (8):
Wozney, J.M., V. Rosen, A.J. Celeste, L.M. Mitsock, M.J. Whitters, R.W. Kriz, R.M. Hewick and E.A. Wang, "Novel Regulators of Bone Formation: Molecular Clones and Activities," Research Articles, Science, vol. 242, pp. 1528-1534 (Dec. 1988).

Other Reference Publication (9):
"Demonstration of Reduced Mitogenic and Osteoinductive Activities in Demineralized Allogeneic Bone Matrix from Vitamin D-deficient Rats", R.T. Turner et al., The Journal of Clinical Investigation, Inc., vol. 82, pp. 212-217 1988.

Other Reference Publication (10):
"Extracellular Matrix Proteins Involved in Bone Induction Are Vitamin D Dependent", T.K. Sampath et al., Biochemical and Biophysical Research Communications, vol. 124, pp. 829-835 1984.

Other Reference Publication (11):
"Vitamin D Is Not Directly Necessary for Bone Growth and Mineralization", J. L. Underwood & H. F. DeLuca, American Journal of Physiology, vol. 246, pp. E493-E498, (1984).

Other Reference Publication (12):
"Vitamin D Metabolites and Endochondral Bone Development", Weintroub, S. and A. H. Reddi, (1991) Int. Congr. Ser. -Excerpta Med., vol. 589, pp. 211-217.

Other Reference Publication (14):
"Recombinant Human Bone Morphogenetic Protein Induces Bone Formation", Wang, et al., Proc. Natl. Acad. Sci. USA, vol. 87, pp. 2220-2224, Mar. 1990.

Other Reference Publication (15):

"Novel Regulators of Bone Formation: Molecular Clones and Activities," Wozney et al., Research Articles, Science, vol. 242, pp. 1528-1534, 1988.

CLAIMS:

1. A method of generating new bone growth in a mammal in need of such treatment comprising administrating to the mammal a bone morphogenetic protein (herein, "BMP") in combination with a Vitamin D compound, wherein the BMP is BMP-2 or BMP-4, and wherein:

a. when the bone morphogenetic protein is BMP-2, from about 500 ng to about 1000 ng BMP-2 is administered in combination with about 6 ng of the Vitamin D compound; and

b. when the bone morphogenetic protein is BMP-4, about 62.5 ng BMP-4 is administered in combination with about 6 ng of the Vitamin D compound.

9. A composition for generating new bone growth in a mammal in need of such treatment, the composition comprising:

a. a Vitamin D compound;

b. a bone morphogenetic protein (herein, "BMP"), wherein the BMP is BMP-2 or BMP-4; and

c. a pharmaceutically-acceptable carrier;

wherein

i. when the bone morphogenetic protein is BMP-2, from about 500 ng to about 1000 ng BMP-2 is administered in combination with about 6 ng of the Vitamin D compound; and

ii. when the bone morphogenetic protein is BMP-4, about 62.5 ng BMP-4 is administered in combination with about 6 ng of the Vitamin D compound.

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